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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,852	07/15/2003	Mark Chee	67234-015	2545

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EXAMINER

TUNG, JOYCE

ART UNIT	PAPER NUMBER
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1637

MAIL DATE	DELIVERY MODE
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09/06/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/620,852

Applicant(s)

CHEE ET AL.

Examiner

Joyce Tung

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 July 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition, under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.
- NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: _____.
- Claim(s) objected to: _____.
- Claim(s) rejected: 35-52.
- Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

The applicant's response to the Office action has been entered. Claims 1-103 are pending. Claims 33-52 are examined.

1. Claims 35-52 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 6, 11, and 13-30 of copending Application No. 10194958 because the terminal disclaimer was not filed.
2. Claims 35, 39, 41, 42, 43, 44, 47, and 49 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 10, 18, 20-22, 23-24, 32, 39-40, 42-46, 54, and 64-66 of copending Application No. 10864935 because the terminal disclaimer was not filed.
3. Claims 35-46 and 49-52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bhatnagar et al. (5,593,840, issued January 14, 1997) in view of Phillip Morris et al. (6,017,738, issued January 25, 2000) and Barany et al. (2002/0150921, issued Oct. 17, 2002).

Bhatnagar et al. disclose a process for amplifying nucleic acid sequence from a DNA or RNA template. The process allows to efficiently detecting a particular point mutation (See the abstract). The process provides primers comprising a first primer which is substantially complementary to first segment at a first end of the target nucleic acid sequence and a second primer, which is substantially complementary to a second segment at a second end of the target nucleic acid sequence. The first and second primers are hybridized to the target nucleic acid sequence (See column 3, lines 11-30). The second primer (oligo 2) is extended and then ligated to the first primer (See fig. 3) to produce fused amplification products (See column 3, lines 31-34). The fused amplification products are amplified (See column 3, lines 35-44). The process also provides four different nucleotide bases (See column 3, lines 27). The amplified fused

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amplification products are detected by detectable signal (See column 7, lines 8-22). The primers may be labeled using a marker (See column 9, lines 17-23, column 15, lines 17-54). The amplified stands may be labeled with different markers (See column 9, lines 24-29). The extension of a primer by polymerase can be blocked (See column 7, lines 32-39).

Bhatnagar et al. do not explicitly disclose linear amplification of the first and second ligated probe to produce first and second amplicons. However, in the disclosure of Bhatnagar et al. the fused amplification product is dissociated from the target nucleic acid sequence and then the fused amplification product is extended by a third primer (See column 3, lines 36-44). It is inherent in the teaching that this step is single primer amplification, which is linear amplification.

Bhatnagar et al. also do not explicitly disclose a universal priming site in a probe. Based on the definition in the specification, the universal priming site means a sequence of the probe, which will bind to a primer for amplification (See 20040121364, [0084]). Thus the features of the primers of Bhatnagar et al. satisfy the limitations of the probe of the instant invention.

Bhatnagar et al. also do not explicitly disclose a second universal priming site in the first probe or second probe. Based upon the discussion above and no physical requirements for the second universal priming site, the first and the second probe are interpreted that the first or second probe has a second universal priming site.

Bhatnagar et al. do not disclose determining a relative amount of the first and second amplicons and the universal priming site comprising a RNA polymerase priming site corresponding to T7, T4 T3, and SP6 RNA polymerase.

Phillip Morris et al. disclose a method for detecting a target nucleic acid sequence in which a first primer hybridizing to the target nucleic acid sequence is immobilized and a second

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primer is provided to hybridize the target nucleic acid sequence in the opposite direction and the second primer is labeled (See the Abstract). The incorporated label in the amplified nucleic acid sequence allows detection and quantification of the amplified nucleic acid (See column 2, lines 1-15). The nucleic acid amplification methods applied to the solid phase amplification process (See column 6, lines 41-58) include NASBA. NASBA amplification method has a transcription step in vitro (See fig. 3). The primer used in NASBA has a RNA promoter sequence corresponding to T7 RNA polymerase (See column 7, lines 12-18). This teaching reads on the limitation recited in claims 36 and 37 in which universal priming site comprises a RNA polymerase priming site corresponding to T7, T4, T3, SP6 RNA polymerase.

One of ordinary skill in the art at the time of the instant invention would have been motivated to apply the method of Bhatnagar et al. to determine the amount of the first amplicon and the second amplicon because as disclosed by the teachings of Philip Morriss et al. the incorporated label in the amplified nucleic acid sequence allows detection and quantification of the amplified nucleic acid (See column 2, lines 1-15). It would have been prima facie obvious to determine the relative amount of the first and the second amplicons for detecting the relative amount of two or more target sequences.

None of the references above discloses the target nucleic acid sequences comprise a solid support, immobilizing the amplification templates or amplicons to a solid support with a capture probe, and that the ligation probes comprise an adapter sequence that differs from the first and second target sequences.

Barany et al. disclose a method for identifying one or more of a plurality of sequence differing by one or more single base changes (See pg. 3, [0027]). The method also provides

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quantitative detection of mutations in a high background of normal sequence (pg. 4, [0035]). The method applies a first oligonucleotide probe having a target specific portion and an addressable array-specific portion and second oligonucleotide probe having a target-specific portion and a detectable reporter label. When hybridized adjacent to one another on a corresponding target nucleotide sequence the first and the second oligonucleotide probe are suitable for ligation together. The ligated products contain the addressable array-specific portion. If there are one or more mismatches, the oligonucleotide probes may hybridize to nucleotide sequence in the sample other than their respective target sequences (See pg. 3, [0028]). After ligation phase, the ligated products are captured on an addressable array in which a capture probe is immobilized at particular sites and the addressable array-specific portion is complementary to the capture probe (See pg. 3, [0029]). It is inherent in the teaching that the probe has a different sequence, which differs from a target (See the Abstract).

One of ordinary skill in the art would have been motivated to apply the addressable array-specific portion to the probe of Bhatnagar et al. used as an adapter sequence because by doing so, the method provides quantitative detection of mutations in a high background of normal sequence (See pg. 4, [0035]). It would have been prima facie obvious to apply the first probe or the second probe with the adapter sequence that comprises different sequences from the target sequences to make the instant invention.

One of ordinary skill in the art would have been motivated to apply the addressable array-specific portion as taught by Barany et al. to the probe of Bhatnagar et al. used as an adapter sequence because by doing so, the method provides quantitative detection of mutations in a high

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background of normal sequence (See pg. 4, [0034]). It would have been prima facie obvious to apply the first probe or the second probe with the adapter to make the instant invention.

The response argues that Bhatnagar et al. do not disclose determining relative amounts of two or more target sequences. However, Barany et al. disclose that fig. 1 shows flow diagrams of the process of the invention compared to a prior art ligase detection reaction using fluorescent quantification (See pg. 6, [0079] and fig.1) and fig. 2 also shows fluorescent quantification using spiked marker compared with mutant allele (See pg. 6, [0081] and fig. 2).

The response also argues that Barany et al. is irrelevant because no immobilized step is claimed. However, the instant claims do not exclude a solid phase assay.

Based upon the analysis above, the rejection is maintained.

4. Claims 47-48 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bhatnagar et al. (5,593,840, issued January 14, 1997) in view of Phillip Morris et al. (6,017,738, issued January 25, 2000) and Barany et al. (2002/0150921, issued Oct. 17, 2002) as applied to claims 35-46 and 49-52 above, and further in view of Akhavan-Tafti (5,998,175, issued December 7, 1999).

The teachings of Bhatnagar et al. Philip Morris et al. and Barany et al. are set forth in section 2 above. Bhatnagar et al., Philip Morris et al. and Barany et al. do not disclose a plurality of pairs of ligation probes with a plurality of target sequences to form a plurality of ligation complexes, each of the plurality comprises more than two and the plurality of probes comprises at least 8, 96, 192, 384, 1152 or 1536.

Akhavan-Tafti discloses a method of synthesizing polynucleotides involving the simultaneous ligation of a set of oligomer 5'-phosphates onto a template-bound primer. The

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ligation is performed with a ligase enzyme (See the abstract). It is inherent in this teaching that a plurality of pairs of ligation probes with a plurality of target sequences is to form a plurality of ligation complexes and each of the plurality comprises more than two (See fig. 2). The disclosure of Akhavan-Taffti also discussed the library can contain all 4^n possible oligomers (See column 5, lines 55-59 and column 6, lines 22-43).

One of ordinary skill in the art would have been motivated to apply a plurality of pairs of ligation probes with a plurality of target sequences to form a plurality of ligation complexes in which the plurality of probes comprises at least 8, 96, 192, 384, 1152 or 1536 as taught by Akhavan-Taffti because the amplification method of Akhavan-Taffti can be use to copy DNA or RNA linearly or exponentially (See column 1, lines 15-17). It would have been prima facie obvious to apply a plurality of pairs of ligation probes with a plurality of target sequences to form a plurality of ligation complexes in which the plurality of probes comprises at least 8, 96, 192, 384, 1152 or 1536.

The response argues the same issues as set forth in section 3 above. Therefore with the same reasons as set forth in section 3 above, the rejection is maintained.

Summary

5. No claims are allowed.
6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (571) 272-0790. The examiner can normally be reached on Monday - Friday, 8:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Joyce Tung *J. Z*
August 30, 2007

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

9/4/07